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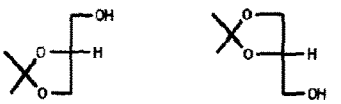
Synthesis of (R) - and (S) - isopropylidene glycerol [1]

Marco Pallavicini[a], Ermanno Valoti[a]*, Luigi Villa[a] and Oreste Piccolo[b]*

[a] Universita` di Milano, Istituto di Chimica Farmaceutica e Tossicologica, viale Abruzzi 42 - 20131 Milano, Italia
[b] "Studio di Consulenza Scientifica", via Borno` 5 - 22080 Sirtori (CO), Italia

Abstract: The preparation of (R)- and (S)-isopropylidene glycerol 1 of high enantiomeric excess (> 98%) was accomplished through salt formation between their hydrogen phthalates with (S)- and (R)-1-methylbenzylamine [MBA] respectively, selective crystallization of these salts and subsequent regeneration of optically active compounds 1 by saponification. The progress of resolution was followed by HPLC analysis on Chiralcel OJ, after converting the hydrogen phthalates into the corresponding mono methyl esters by diazomethane.

The development of efficient syntheses of enantiomerically pure chiral C_3 synthons is the subject of intense current study. These compounds are useful starting materials for the preparation of optically active β-blockers, centrally-acting antihypertensives, antiglaucoma agents, an antitussive drug and glycerophospholipids.



(R)-1 (S)-1

Compounds 1 of enantiomeric excess > 95% are usually obtained starting from carbohydrates, such as for example (D)-mannitol and (L)-ascorbic acid, or aminoacids, such as for example (L)-serine[2,3]; however the same synthetic strategy is not convenient for the preparation of both enantiomers, due to the high cost of unnatural raw material.

Enantioselective microbiological oxidation of racemic 1 was described to obtain (R)-1 in

very high enantiomeric excess (> 97%) together with (R)-isopropylidenglyceric acid (e.e. 92%), from which (S)-1 of the same enantiomeric excess could be obtained through reduction by hydrides[4].

Another strategy to optically pure 1 includes a biocatalytic reduction of 1-acetoxy-3-benzyloxy-propanone as the key step, the optically active corresponding 1-acetoxy-3-benzyloxy-2-propanol being then manipulated to give (R)- or (S)-1[5].

Numerous attempts to resolve efficiently racemic 1 by enantioselective hydrolysis of the corresponding alkanoate or by esterification of (RS)-1, catalyzed by commercial available lipases or esterases were elusive (e.e's usually < 65% were obtained)[6,7] or it was difficult to duplicate the highest reported e.e. (80-95%)[8,9,10] obtained by using not easily available lipases. Finally an efficient procedure to obtain (S)-1 was also reported by inclusion crystal formation with host compounds prepared from natural tartaric acid[11].

Here we report an easier procedure to obtain both (R)- and (S)-1 (e.e. > 98%) in fair yields, by resolution of the corresponding hydrogen phthalates with (S)- and (R)-1-methylbenzylamine [MBA] respectively (see scheme). Quite surprisingly this procedure had not been investigated up to now.

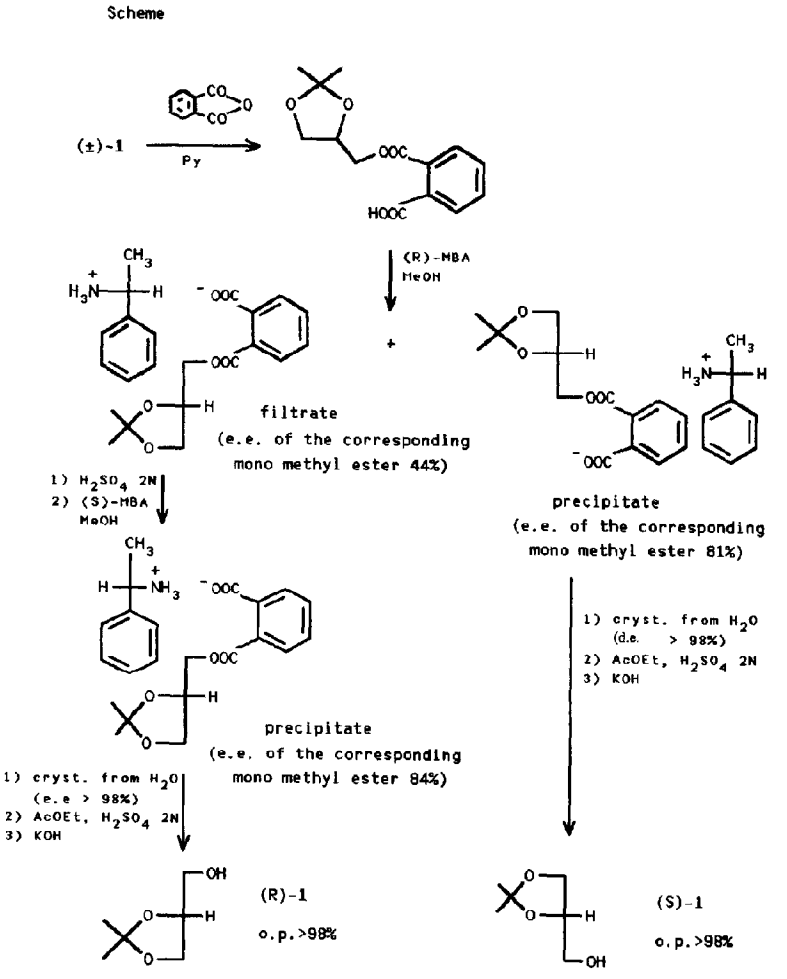
The crude oily hydrogen phthalate of (RS)-1[12] [54.5 g; 0.194 mol], prepared in a nearly quantitative yield from (RS)-1 [25.9 g; 0.197 mol] and phthalic anydride [29.2 g; 0.197 mol] in dry pyridine [20 ml] according to the usual procedure and work up[13], was diluted in methanol [260 ml] and treated at 50°C with (R)-MBA [Aldrich; 23.5 g; 0.194 mol]. After slow cooling at about 10°C, the precipitate was filtered and washed with cold methanol to give 27.6 g of the corresponding salt[14], $[\alpha]_D^{20}$ +11.5 (c=2.5, MeOH)(d.e. 81%, e.e. determined on the corresponding mono methyl ester (prepared by diazomethane), by HPLC on a Chiralcel OJ column (250 x 4.6 mm I.D.) from Daicel, using n.hexane/i.propyl alcohol 92/8 as eluent (flow-rate 0.6 ml/min) at 254 nm)[15]. After a crystallyzation from water [310 ml], 16.8 g of salt, $[\alpha]_D^{20}$ +14.5 (c=2.5, MeOH)(d.e. > 98%), was recovered and suspended in ethylacetate [150 ml]. After removal of MBA by acidic washing with H_2SO_4 2N, the solvent was evaporated under vacuum and the residue saponified by KOH [10 g] in water [70ml]. S-1 was extracted from water with ethyl acetate; the organic phase was concentrated and the residue was distilled under vacuum to give 5.3 g of (S)-1[16], α_D^{20} +15.1 (l=0.1, neat); $[\alpha]_D^{20}$ +21.8 (c=1, ethanol)(o.p. > 98%, on the basis of the maximum rotatory power reported in the literature)[2].

The methanolic mother waters of the first precipitation were concentrated and the residue worked up to afford about 34.6 g (0.124 mol) of crude hydrogen phthalate of (R)-1 (e.e. 44%). It was diluted in methanol [145 ml] and treated with (S)-MBA [Aldrich; 15 g; 0.124 mol]. After the analogous treatment 4.2 g of (R)-1[16], $[\alpha]_D^{20}$ -21.7 (c=1, ethanol)(o.p. > 98%) was recovered.

This procedure was improved and scaled up to the ton scale[17]. Also other protected glycerol derivatives such as the corresponding cyclohexylidene ketals were resolved with e.e. > 95%, through their hydrogen phthalates by using (R)- and (S)-MBA[1].

Synthesis of (*R*)- and (*S*)-isopropylidene glycerol

Scheme



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[12] ^{1}H NMR ($CDCl_3$): δ ppm 8.85 (s, 1 H), 8.2-7.4 (m, 4 H), 4.7-3.7 (m, 5 H), 1.45 (s, 3 H) and 1.4 (s, 3 H).
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[14] ^{1}H NMR (DMSO): δ ppm 7.8 (m, 1 H), 7.6-7.3 (m, 8 H), 4.4 (m, 2 H), 4.2 (d, 2 H), 4.1 (dd, 1 H), 3.8 (dd, 1 H), 1.6 (d, 3 H), , 1.4 (s, 3 H), 1.3 (s, 3 H).
[15] Under these conditions the retention times of the methyl phthalates of (S)-1 and (R)-1 were 38.68 and 43.04 minutes respectively.
[16] ^{1}H NMR ($CDCl_3$): δ ppm 4.2 (m, 1 H), 4.0 (dd, 1 H), 3.6-3.4 (m, 3 H), 2.4 (br s, 1H), 1.4 (s, 3 H), 1.3 (s, 3 H).
[17] (R)- and (S)-1 are produced by Chemi S.p.a., viale F.Testi 117, 20092 Cinisello Balsamo (MI), Italia.

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